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TITLE: Vaccination with Dendritic Cell Myeloma Fusions in Conjunction with Stem Cell Transplantation and PD-1 Blockade

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14. ABSTRACT
Most patients with multiple myeloma achieve a complete or near complete response following autologous transplantation. However, patients experience disease relapse from a persistent reservoir of chemotherapy resistant disease. There has been strong interest in developing immunotherapeutic strategies to eradicate residual disease following autologous transplantation. Our group has developed a tumor vaccine model whereby dendritic cells are fused with tumor cells. In clinical trials, vaccination with fusion cell results in anti-tumor immune and disease responses in a subset of patients. However, vaccine efficacy is blunted by tumor mediated immune suppression and the increased presence of regulatory T cells characteristic of patients with malignancy. An important element contributing to tumor mediated immune suppression is the PD-1/PDL-1 pathway. PD-L1 exerts a significant role in promoting T cell tolerance by binding PD-1 on activated T cells and suppressing their capacity to secrete stimulatory cytokines. We have demonstrated that blockade of this pathway results in enhanced immune responses to DC/myeloma fusion cells ex vivo. In the proposed study, we will examine toxicity, immunologic effect and clinical efficacy of CT-011 therapy following stem cell transplantation for patients with myeloma. These endpoints will then be assessed in patients undergoing combined therapy with the vaccine and antibody.

15. SUBJECT TERMS
DC/myeloma fusion vaccine, PD1 blockade, immunotherapy, multiple myeloma

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Progress Report
P.I.: David Avigan
July 2011

I. Introduction:

We have initiated a clinical trial in which patients with multiple myeloma are treated with PD-1 blockade alone (Cohort 1) and in conjunction with a dendritic cell/myeloma fusion cell vaccine (Cohort 2) following autologous transplantation. The goal of the project is determine the effect of PD-1 blockade on the capacity of the dendritic cell (DC)/multiple myeloma (MM) fusions to stimulate effective anti-tumor immunity and disease response. We have previously demonstrated that vaccination with DC/ MM fusions potently induces cellular and humoral anti-tumor immune responses[1]. However, vaccine efficacy is blunted by the immunosuppressive milieu characteristic of patients with malignancy. A key component of this immunosuppressive environment is the presence of regulatory T cells that are increased in the circulation, tumor bed and draining lymph nodes of patients with malignancy[2-4]. We have shown that vaccine responses are augmented following autologous transplantation due to depletion of regulatory T cells and the associated transient reversal of tumor mediated tolerance. Another key component of tumor mediated immune suppression is the increased signaling via the PD-1/PDL-1 pathway[5,6]. This pathway is upregulated in the setting of chronic viral infection and malignancy and results in an exhausted T cell phenotype[7,8]. In the present project, we plan to examine the effect of PD-1 blockade on vaccine efficacy. We are conducting a clinical trial in which patients with multiple myeloma undergoing stem cell transplantation will undergo serial administration of CT-011 antibody post-transplant alone (Cohort 1) or in conjunction with vaccination with DC/MM fusions (Cohort 2).

II. Body

Pre-clinical Data:

Pre-clinical studies evaluating the effect of PD-1 blockade on immune response to DC/myeloma fusion cells in vitro were summarized in the yearly progress report submitted in May 2010. Results of pre-clinical studies have subsequently been published (see section IV: Reportable Outcomes).

Clinical Trial:

The clinical study will be conducted in two stages. In the first stage, a pilot study will be conducted in which patients are treated with CT-011 alone following autologous transplant. The primary objective of this stage is to explore immunologic responses to CT-011 in the post-transplant period. The secondary objective is to assess the toxicity of treating patients with CT-011 in the post-transplant setting.

In the second stage, patients will receive a combination of CT-011 and DC/myeloma fusion vaccination. The primary objective is to determine if cellular immunity is induced by treatment with monoclonal antibody CT-011 and DC/myeloma fusion cells in conjunction with stem cell transplant. The secondary objectives of this stage are: 1) To assess the toxicity associated with treating multiple myeloma patients with monoclonal antibody CT-O11 in combination with DC/myeloma fusion vaccine following autologous

transplant, 2) To correlate levels of circulating activated and regulatory T cells with immunologic response, and 3) To define anti-tumor effects using serum markers, radiological studies, and time to disease progression.

Study Population: The targeted study population includes patients with multiple myeloma who are potential candidates for high dose chemotherapy with stem cell rescue. On April 25, 2011, the study received IRB approval to increase study enrollment to cohort 1 to a maximum of 20 participants. When 10 participants in cohort 1 have received two infusions of CT-011, enrollment to cohort 2 will begin. Cohort 2 will enroll 25 evaluable participants. In cohort 1, participants will receive three infusions of CT-011 at doses of doses of 3mg/kg given at 6 week intervals beginning 1-3 months following autologous transplant. In cohort 2, participants will receive three infusions of CT-011 given at six week intervals, in conjunction with vaccination with DC/myeloma fusion cells. Vaccination will be given one week before each infusion of CT-011 and will be given in conjunction with GM-CSF on the day of vaccination and for three days thereafter.

Status: The protocol (DF-HCC protocol number 09-061) is open to accrual at the DF/HCC as of March 19, 2010; Rambam Medical Center (RMC), Haifa, Israel was added on April 26, 2011.

As of July 29, 2011, 18 patients have been screened. There have been five screen failures: four patients did not meet eligibility criteria and one patient elected to pursue only standard of care therapy. In total, 13 participants met eligibility criteria and have been enrolled: 11 participants at DF/HCC and two participants at RMC. Of the subjects who were enrolled at DF/HCC, two have completed treatment and are now in active follow-up; one is currently receiving treatment; two have completed autologous stem cell transplants and will initiate treatment between 30-100 days following transplant; four have undergone tumor collection for DTH skin testing and are completing pre-transplant chemotherapy. Of the two subjects who were enrolled at RMC, both have undergone tumor collection for DTH skin testing and are completing induction chemotherapy.

Two participants were removed from study at DF/HCC during pre-transplant therapy, prior to initiation of study treatment. One subject had disease progression. The second participant died after suffering a cardiac arrest in his home. Although the event did not meet reporting criteria to the FDA, the event was nevertheless communicated to the FDA on 11/14/10 (1571: S268) as it was representative of a death on study.

Subject Study Information:

A. SCREEN FAILURES

Subject Initials	Screening Number	Consent Date	Age	Gender	Race	Reason
ES	2	5/25/2010	54	F	White	Failure to meet eligibility criteria
JP	5	7/16/2010	51	M	Hispanic	Failure to meet eligibility criteria
GW	7	10/28/2010	59	M	White	Failure to meet eligibility criteria
JD	13	11/30/1959	51	M	White	Failure to meet eligibility criteria
EB	18	07/25/11	62	F	African American	Elected to pursue standard of care therapy only

B. SUBJECTS ENROLLED

Subject Initials	Screening Number	Enrollment Number	Consent Date	Registration Date	Age	Gender	Race	Off Study Date	Reason Off-Study
LC	1	1	5/10/2010	5/13/2010	48	M	White	8/14/10	Disease Progression
RG	3	2	6/23/2010	7/2/2010	70	M	White	11/5/10	Death
RP	4	3	7/1/2010	7/9/2010	52	F	Black	N/A	N/A
CC	6	4	9/16/2010	9/29/2010	55	M	White	N/A	N/A
KF	8	5	12/21/2010	12/30/2010	55	F	White	N/A	N/A
DW	9	6	12/27/2010	1/7/2011	47	M	White	N/A	N/A
DF	10	7	12/29/2010	1/13/2011	63	M	White	N/A	N/A
GF	11	8	1/3/2011	1/28/2011	73	F	White	N/A	N/A
SM	12	9	2/4/2011	2/15/2011	58	M	White	N/A	N/A
RR	14	10	5/16/11	5/18/11	67	M	White	N/A	N/A
AG	15	11	5/26/11	6/6/11	45	F	White	N/A	N/A
KI	16	12	6/9/11	6/14/11	61	M	White	N/A	N/A
BF	17	13	7/19/11	7/21/11	64	F	White	N/A	N/A

C. SUBJECTS TREATED WITH AT LEAST ONE INFUSION/VACCINE AT DF/HCC

SUBJECT ID	Cohort and Dose Administered	Treatment Dates	Clinical Outcome
RP/PM3	Cohort 1 3 doses at 3mg/kg	#1. 2/14/11 #2. 3/28/11 #3. 5/9/11	Best response at the end of transplant was complete response. Since completing treatment, the subject has remained in a complete response.
CC/PM4	Cohort 1 3 doses at 3mg/kg	#1. 5/4/11 #2. 6/15/11 #3.7/27/11	Best response at the end of transplant was near complete response. Subject completed treatment and will have disease restaged at 1 month following completion of treatment.
KF/PM5	Cohort 1 3 doses at 3mg/kg	#1 6/28/11 #2. TBD #3. TBD	Best response at the end of transplant was complete response. Subject is in the treatment phase of the study and will have disease restaged at 1 month following completion of treatment.

D. TREATMENT RELATED ADVERSE EVENTS AT DF/HCC

Subject ID	AE	Onset	CTC Grade	Relationship	Action Taken Regarding TX	Outcome
PM03	LEUKOPENIA	3/14/11	1	POSSIBLE	NONE	RESOLVED
PM03	LEUKOPENIA	5/2/11	1	POSSIBLE	NONE	RESOLVED
PM03	LEUKOPENIA	5/23/11	1	POSSIBLE	NONE	RESOLVED
PM03	LEUKOPENIA	7/11/11	2	POSSIBLE	NONE	RESOLVED
PM03	LEUKOPENIA	7/13/11	1	POSSIBLE	NONE	ONGOING
PM03	ANC	5/9/11	1	POSSIBLE	NONE	RESOLVED
PM03	ANC	5/23/11	1	POSSIBLE	NONE	RESOLVED
PM03	ANC	6/10/11	2	POSSIBLE	NONE	RESOLVED
PM03	ANC	7/11/11	3	POSSIBLE	NONE	RESOLVED
PM03	ANC	7/13/11	1	POSSIBLE	NONE	ONGOING
PM03	ALLERGIC RHINITIS	7/11/11	1	POSSIBLE	NONE	ONGOING
PM04	DIARRHEA	5/5/11	1	PROBABLE	NONE	RESOLVED
PM04	DIARRHEA	5/19/11	1	PROBABLE	NONE	RESOLVED
PM05	DIARRHEA	7/7/11	1	POSSIBLE	NONE	RESOLVED

Treatment Related Serious Adverse Events: None.

Treatment Summary of Subjects that Died While on Study: Not Applicable. There has been one death on study. However, the participant had not initiated study treatment**.**

III. Key Research Accomplishments:

- Pre-clinical studies demonstrating increased PD1 expression on T cells isolated from patients with multiple myeloma, and enhanced immune response to DC/tumor fusion vaccination in the presence of PD1 blockade have been published (Rosenblatt et al, J Immunother;34:409-418)
-A clinical is being conducted in which patients are treated with CT-011 alone following autologous transplant (Cohort 1), and in conjunction with DC/myeloma fusion vaccination (Cohort 2). The study is currently open to enrollment at both the Dana Farber Harvard Cancer Center (Boston, Ma) and Rambam Medical Center (Haifa, Israel). 13 patients have been enrolled onto the study to date.

IV. Reportable Outcomes:

Rosenblatt J, Glotzbecker B, Mills H, et al. PD-1 Blockade by CT-011, Anti-PD-1 Antibody, Enhances Ex Vivo T-cell Responses to Autologous Dendritic Cell/Myeloma Fusion Vaccine. J Immunother. 2011;34:409-418.

V. Conclusions:

Results of our pre-clinical studies demonstrating that PD-1 blockade in conjunction with DC/tumor fusion cell stimulation results in a skewing toward Th1 rather than Th2 cytokine secretion, decreased regulatory T cell expansion, and enhanced killing of autologous tumor, have been recently published in the Journal of Immunotherapy. The clinical trial (DF-HCC protocol 09-061) is open to accrual at both the Dana Farber Harvard Cancer Center (Boston), and Rambam Medical Center (Haifa, Israel). 13 patients are currently enrolled on the clinical trial. We anticipate that the first 10 evaluable patients will have completed their follow up period in the next 12 months, and enrollment to the second cohort will then be initiated. Enrollment to the second cohort will take place over the subsequent 12 months.

VI. References:

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VII. Appendices:

Appendix 1: Citation and abstract of publication attached

Appendix 1

PubMed

Display Settings: Abstract

J Immunother. 2011 Jun;34(5):409-18.

PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine.

Rosenblatt J, Glotzbecker B, Mills H, Vasir B, Tzachanis D, Levine JD, Joyce RM, Wellenstein K, Keefe W, Schickler M, Rotem-Yehudar R, Kufe D, Avigan D.

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Abstract

We have developed a cancer vaccine in which autologous tumor is fused with dendritic cells (DCs) resulting in the presentation of tumor antigens in the context of DC-mediated costimulation. In clinical trials, immunologic responses have been observed, however responses may be muted by inhibitory pathways. The PD1/PDL1 pathway is an important element contributing to tumor-mediated immune suppression. In this study, we demonstrate that myeloma cells and DC/tumor fusions strongly express PD-L1. Compared with a control population of normal volunteers, increased PD-1 expression was observed on T cells isolated from patients with myeloma. It is interesting to note that after autologous transplantation, T-cell expression of PD-1 returned to levels seen in normal controls. We examined the effect of PD-1 blockade on T-cell response to DC/tumor fusions ex vivo. Presence of CT-011, an anti-PD1 antibody, promoted the vaccine-induced T-cell polarization towards an activated phenotype expressing Th1 compared with Th2 cytokines. A concomitant decrease in regulatory T cells and enhanced killing in a cytotoxicity assay was observed. In summary, we demonstrate that PD-1 expression is increased in T cells of patients with active myeloma, and that CT-011 enhances activated T-cell responses after DC/tumor fusion stimulation.

PMID:21577144[PubMed - in process] PMCID: PMC3142955[Available on 2012/6/1]

Publication Types, Grant Support

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